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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER SGAGIAS, MAGDALENE K				
ART UNIT 1632		PAPER NUMBER		
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/588,573

**Applicant(s)**

RAZ ET AL.

**Examiner**

Magdalene K. Sgagias

**Art Unit**

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 09 January 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1 and 3-24 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1 and 3-24 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-8508)
- 4) ☐ Interview Summary (PTO-413)
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_
- Paper No(s)/Mail Date \_\_\_\_\_

### **DETAILED ACTION**

Claims 1, 3-24 are pending and under consideration. Claim 2 is canceled. The amendment has been entered. Applicant's election of species has been acknowledged. Applicants elected synthetic nucleic acid; phosphorothioate internucleotide linkage; and complexed with a microcarrier for claim 36;

#### ***Claim Objections***

Claim 1 objection to because the claim is directed to a nucleic acid that exists in nature and not to an isolated nucleic acid or a nucleic acid encoding a gene product is withdrawn in view of the amendment.

#### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-24 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method of treating irritable bowel syndrome (IBS) in an individual, the method comprising administering to the individual an effective amount of a therapeutic nucleic acid to reduce at least one symptom of IBS in the individual, wherein the therapeutic nucleic acid is non-coding, wherein the therapeutic nucleic acid is isolated or

synthetic, and wherein the therapeutic nucleic acid comprises an unmethylated 5'-CG-3' nucleotide sequence.

The specification nebulously discusses treating irritable bowel syndrome (IBS) in an individual suffering from IBS by administering to the individual an effective amount of a therapeutic nucleic acid and further by administering at least a second therapeutic agent [0017] (and throughout the specification). However, the specification fails to provide any guidance and/or working examples or any data at all for administering any nucleic acid at an effective level for treating IBS. Thus, as enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the claimed method for treating IBS. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

The claims embrace a method for treating IBS in an individual by administering any type of nucleic acid resulting in the production of a therapeutic protein in a bowel tissue. The specification failed to provide specific guidance or working examples correlating to treatment of IBS one of skill in the art could not rely on the state of the gene therapy art to treat IBS by way of the claimed methods. At the time of filing the art of gene therapy was an unpredictable art with respect cell targeting, levels of expression of a therapeutic protein necessary to provide therapy, and mode of administration of the therapeutic gene. Numerous factors complicate the nucleic acid delivery art, which would not have been shown to overcome by routine experimentation. These include the fate of the DNA itself (volume of distribution, rate of clearance into tissues, etc).

With regard to the administration of a therapeutic nucleic acid comprising a nucleotide sequence of the formula 5'-CG-3' for treatment of IBS for example, the art teaches that for example administration of 5'-CpG-3' oligonucleotides is unpredictable. **Shanahan et al** (Am J

Physiol Gastrointest Liver Physiol 288:417-421, 2005 (IDS)) teach in certain murine models of IBD, bacterial CpG DNA mediates the anti-inflammatory effect by signaling through host TLR9 receptors (p G420, 1<sup>st</sup> column). CpG DNA motifs may have opposing effects in experimental models of intestinal inflammation depending on the timing of its administration. In contrast to the prophylactic effect of CpG DNA before the onset of inflammation, exposure to CpG DNA during acute inflammation has been shown to exacerbate disease in a murine model of IBD (p G420, 1<sup>st</sup> column). **Watson et al**, (Clinica Chimica Acta, 364: 1 – 11, 2006 (IDS)) while reviewing the status of the CpG oligonucleotides used to induce suppression of the immune hyperactivity of the GI tract note that "For some cell types direct activation by CpG ODN is controversial, and may require co-factors: for instance, recently it has been demonstrated that human peripheral NK cells express TLR9 mRNA but functionally respond to CpG ODN (B-type) stimulation only when prestimulated with IL-12 or IL-8 (p 3, 2nd column). Watson also notes "characterization of synthetic ODN raises a number of pertinent issues. Since the synthetic PS-ODN and the natural PO-ODN have different stimulatory properties, one must exercise caution in transposing the effects of CpG-B ODN in a model system to a generalized effect of bDNA. Similarly, the degree of bacterial DNA methylation might represent an important contributing factor to how stimulatory the bacterial DNA is in vivo. Interestingly, nucleotide motifs either within or on discrete CpG ODNs that dramatically reduce the immunostimulatory properties of activatory CpG ODNs have been identified, raising the question of how the eukaryotic cell distinguishes different bacterial DNA sequences. Genomic sequencing and comparison of pathogen versus commensal DNA is required to address this question. Thus, functionally, the effect of CpG DNA is modulated by base sequence, presence of CpG motifs, and, artificially, by modification of the phosphodiester backbone" (p 3-4). Thus, the therapeutic efficacy of 5'-CpG-3' nucleic acid treatment of IBS is unpredictable. Hence, one of skill in the art cannot predict the

therapeutic effects of the formula 5'-CpG-3' nucleic acids in IBS since it appears to depend on the route of administration, dose and timing of administration of the CpG DNA motifs and exposure to CpG DNA has been shown to be associated with the onset of inflammation and its association with the host's immune response resulting in a therapeutic effect in vivo is not conclusive as raised by the state of the art at the time of filing. The disclosure has not taught the therapeutic effects of nucleic acids comprising unmethylated 5'-CpG-3' in IBS disease when they are administered via any route at any dose.

In light of the above, it appears that the state of the art is suggesting that nucleic acid and the formula of 5'-CG-3' IBS therapy might be feasible in the future. The instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of route and dose of administration of a therapeutic nucleic acid for effective IBS therapy raised by the state of the art. The quantity of experimentation required to practice the methods as claimed would require the de novo determination of effective target sites, modes of delivery, safe administration of the oligonucleotide and timing of administration of CpG oligodeoxynucleotides to target appropriate cells and/or tissues in a subject, and further whereby treatment effects are provided for the claimed condition therefore, the skilled artisan would conclude that the state of art of nucleic acid or of the formula of 5'-CG-3' therapy is undeveloped and unpredictable at best.

Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for treating IBS by nucleic acid or of the formula of 5'-CG-3' therapy without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the treatment of IBS, particularly with any nucleic acid or of the formula of 5'-CG-3', the lack of direction or guidance provided by the specification for the

treatment of IBS, particularly with any nucleic acid or of the formula of 5'-CG-3', the absence of working examples that correlate to the treatment of IBS, the unpredictable state of the art with respect to the treatment of IBS, particularly with any nucleic acid or of the formula of 5'-CG-3', the undeveloped state of the art pertaining to for the treatment of IBS, particularly with any nucleic acid or of the formula of 5'-CG-3', and the breadth of the claims directed to all types of IBS, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

A. Applicants argue that Barbara does not teach that "administration of 5'-CG-3' is unpredictable." Instead, Barbara reviews references that explore the hypothesis on the role of low grade inflammation in IBS. Barbara does not even mention the possibility of using a therapeutic nucleic acid in the treatment of IBS. As such, Barbara does not support the assertion that "the art teaches that for example administration of 5'-CG-3' is unpredictable." These arguments are partly convincing for not teaching administration of administration of 5'-CG-3' but Barbara teaches the role of low grade inflammation in IBS and the Barbara reference is withdrawn.

B. Applicants argue that Shanahan teaches that in certain routine models of IBD, bacterial CpG DNA mediates the anti-inflammatory effect by signaling through host TLR9 receptors. Applicants argue IBS is not the same condition as IBD. Shanahan relates to IBD. As such, in contrast to the Office Action's assertion, Shanahan does not teach that "therapeutic efficacy of 5'-CpG-3' nucleic acid treatment of IBS is unpredictable."

These arguments are not persuasive because a gastrointestinal inflammation embraces irritable bowel syndrome. It is well known in the art and there is evidence of inflammation in the IBS. It is well known that IBS is associated with altered gastrointestinal physiology and hypersensitivity. For example, **Barbara et al**, [Gut, 51(Suppl 1):i41-i44, 2002 (IDS)] note that

low grade mucosal inflammation in irritable bowel syndrome (IBS) due to an increased number of inflammatory cells in the colonic and ileal mucosa as a result of episodes of infectious enteritis and changes in bacterial microflora may all play a role in promoting and perpetuating this low grade inflammatory process (abstract). Barbara et al note altered interactions between the mucosal immune system and the afferent nerve terminals which project into the intestinal mucosa has been found in patients with visceral hypersensitivity and in cases of IBS (p 141, 2nd column. 2nd paragraph). Barbara also notes abnormal neuroimmune interactions may contribute to the altered gastrointestinal physiology and hypersensitivity that underlies IBS thus IBS is associated with intestinal inflammation and infections in the pathogenesis of IBS is given (abstract). Thus, the art teaches that gastroinflammatory disorders include IBS.

C. Applicants argue the Office Action cited passages in Watson in which various aspects of CpG ODNs were discussed. Applicants argue Watson does not specifically discuss the effect of a therapeutic nucleic acid comprising the sequence 5'-CG-3' on treating IBS. Watson reviews the literature relating to 5'-CG-3' in treating gastroinflammatory disorders such as IBD, Crohn's disease, etc. As explained above, gastroinflammatory disorders are not the same as IBS. As such, Watson does not teach that "therapeutic efficacy of 5'-CpG-3' nucleic acid treatment of IBS is unpredictable."

These arguments are not persuasive for the same reasons discussed above that IBS is associated with gastroinflammatory disorders such as IBD according to the teachings of Barabara.

D. Applicants argue the specification provides ample disclosure such that those skilled in the art could carry out a subject method without undue experimentation. The instant specification states that a therapeutic nucleic acid can be administered to a subject prior to the onset of symptoms (e.g., prior to abdominal pain, or after onset of symptoms (e.g., after onset of

abdominal pain, after onset of constipation, after onset of diarrhea). Specification, paragraph 0022. The instant specification states that animal models of IBS are known in the art. Specification, paragraph 0021. The instant specification describes how to determine efficacy of a therapeutic nucleic acid in treating IBS. The instant specification states that the Rome criteria can be used, and provides a reference that describes the Rome criteria. Specification, paragraph 0019. The instant specification states that effective amounts of a therapeutic nucleic acid are amounts that are effective to reduce at least one symptom of IBS, e.g., abdominal pain, constipation, and diarrhea. Specification, paragraph 0018. The specification states that exemplary effective amounts of a therapeutic nucleic acid are in the range of from about 1 ug to about 500 ug. Specification, paragraphs 0030-0034 and paragraph 0076. Furthermore, the specification provides ample guidance as to particular sequence motifs present in a therapeutic nucleic acid. Specification, paragraphs 0043-0064. In view of the ample description in the specification, and the knowledge in the art, those skilled in the art could readily carry out a claimed method without undue experimentation. Thirdly, compliance with the enablement requirement under 35 U.S.C. § 112, first paragraph, does not require or mandate that a working example be disclosed. The specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice the invention without undue experimentation.

These arguments are not persuasive because the prior art has shown that for example, the synthetic PS-ODN and the natural PO-ODN have different stimulatory properties, one must exercise caution in transposing the effects of CpG-B ODN in a model system to a generalized effect of bDNA. Similarly, the degree of bacterial DNA methylation might represent an important contributing factor to how stimulatory the bacterial DNA is in vivo. Interestingly, nucleotide motifs either within or on discrete CpG ODNs that dramatically reduce the immunostimulatory

properties of activatory CpG ODNs have been identified, raising the question of how the eukaryotic cell distinguishes different bacterial DNA sequences. Thus, one could not simply mimic the treatment for IBS and expect to work on this disease. Given the specification nebulously discusses treating irritable bowel syndrome (IBS) in an individual suffering from IBS by administering to the individual an effective amount of a therapeutic nucleic acid and further by administering at least a second therapeutic agent the ordinary artisan would be required to begin art square one, that is, generating data. The ordinary artisan would be required to administer the claimed composition to a diverse distinct accepted animal models including humans, calculate the effective doses, if effective at all, and ascertain the results accordingly until a sufficient amount of data is collected. It is not clear as discussed above the issues of the art would be worked out. For the reasons above, it would require undue experimentation for one of skill in the art to make and use the claimed invention.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 14-15, 17 rejection under 35 U.S.C. 102(b) as being anticipated by Vesely et al, (US 5,716,615; Feb 10, 1998) is withdrawn in view of the amendment.

***Claim Rejections - 35 USC § 103/Necessitated by amendment***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 5-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over

**Schwartz et al** (WO 98/55495) in view of **Fearon et al** (US 2003/0133988); **Barbara et al**, [Gut, 51(Suppl 1): i41-i44, 2002 (IDS)]; **Nobaek et al** (The American Journal of Gastroenterology, 95(5): 1231-1238, 2000).

To the extent the claims are directed to an isolated or synthetic nucleic acid the following rejection is appropriate.

**Schwartz et al** teach isolated or synthetic oligonucleotides (ODNs) that comprise unmethylated 5' -CG-3' nucleotide sequences and also provides for a methods of treating individuals in need of immune modulation comprising administration of a composition comprising an immunostimulatory (ISS) ODN that contains at least one ISS, to individuals suffering from cancer, allergic diseases, infectious diseases, individuals infected with hepatitis B virus, papillomavirus, and human immunodeficiency virus, infection by hepatitis B virus, influenza virus, herpes virus, human immunodeficiency virus and papillomavirus, infectious disease due to bacterial infection, including those diseases due to infection by Hemophilus influenza, Mycobacterium tuberculosis and Bordetella pertussis and asthma (p 4-5) (claim 1). Schwartz teaches routes of administration include but are not limited to topical, dermal, transdermal, transmucosal, epidermal parenteral, gastrointestinal, and naso-pharyngeal and pulmonary, including transbronchial and transalveolar (p 24-27, 44-45) (claims 5-8). Schwartz teaches modifications of ISS include modifications of the 3'OH or 5'OH group, modifications of the nucleotide base, modifications of the sugar component, and modifications of the phosphate group (claim 20). Schwartz teaches the phosphorous derivative (or modified phosphate group) which can be attached to the sugar or sugar analog moiety in the oligonucleotides of the present

invention can be a phosphorothioate, phosphorodithioate or the like, a phosphorothioate linkage can be used in place of a phosphodiester linkage because oligonucleotides with phosphorothioate backbones can be more immunogenic than those with phosphodiester backbones and appear to be more resistant to degradation after injection into the host (claim 21). Schwartz teaches the nucleic acid is complexed with microcarrier oils, creams and ointments applied directly to the skin or incorporated into a protective carrier such as a transdermal device (so-called "patch"), suitable creams, ointments, non-lipid polymers, such as a synthetic polycationic amino polymer, liposomes and microparticles, including but not limited to, polystyrene, starch, polyphosphazene and polylactide/polyglycosides (claims 22-24). Schwartz teaches the nucleic acid has of any length greater than 6 bases or base pairs, preferably greater than 15 bases or basepairs, more preferably greater than 20 bases or base pairs in length (claim 19). Schwartz differs from the present invention for not teaching treating irritable bowel syndrome (IBS).

However, at the time of the instant invention, **Fearon et al**, teaches administration of immunomodulatory polynucleotide/microcarrier complexes comprising 3-6 mer immunomodulatory oligonucleotides complexed covalently of non-covalently bound in a microcarrier (abstract). Fearon teaches methods of increasing at least one Th1-associated cytokine in an individual, including IL-2, IL-12, TNF-beta, and IFN-gamma in an individual, particularly in an individual in need of increased IFN-gamma levels, by administering an effective amount of an IMO/MC complex or encapsulate to individuals having disorders which respond to the administration of IFN-gamma. such disorders include a number of inflammatory disorders including, but not limited to, ulcerative colitis [0153]. Barbara et al, supplements the teachings of Fearon by teaching a role of inflammation in irritable bowel syndrome (title). **Barbara et al**, [Gut, 51(Suppl I):i41-i44, 2002 (IDS)] note that low grade mucosal inflammation

in irritable bowel syndrome (IBS) due to an increased number of inflammatory cells in the colonic and ileal mucosa as a result of episodes of infectious enteritis and changes in bacterial microflora may all play a role in promoting and perpetuating this low grade inflammatory process (abstract). Barbara et al note altered interactions between the mucosal immune system and the afferent nerve terminals which project into the intestinal mucosa has been found in patients with visceral hypersensitivity and in cases of IBS (p 141, 2nd column. 2nd paragraph). Barbara also notes abnormal neuroimmune interactions may contribute to the altered gastrointestinal physiology and hypersensitivity that underlies IBS thus IBS is associated with intestinal inflammation and infections in the pathogenesis of IBS is given (abstract). **Nobaek et al** (The American Journal of Gastroenterology, 95(5): 1231-1238, 2000) teaches alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with Irritable Bowel Syndrome (IBS) (title). Nobaek teaches the administration of *Lb. plantarum* with known probiotic properties decreased pain and flatulence in patients with IBS (p 1231, 2<sup>nd</sup> column 1<sup>st</sup> paragraph). The fiber content of the test solution was minimal and it is unlikely that the fiber content could have had any effect. Nobaek suggests this type of probiotic therapy warrants further studies in IBS patients (p 1231, 2<sup>nd</sup> column 1<sup>st</sup> paragraph). As such Nobaek et al provide sufficient motivation for one of ordinary skill in the art to apply the unmethylated 5' -CG-3' nucleotide sequences technology of Scharztz for treating IBS with associated with intestinal inflammation.

Accordingly, in view of the teachings of Fearon et al, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the unmethylated 5' -CG-3' nucleotide sequences technology of Schwartz by use of of immunomodulatory polynucleotide/microcarrier complexes comprising 3-6 mer immunomodulatory oligonucleotides complexed covalently of non-covalently bound in a

microcarrier as taught by Fearon further comprising *Lb. plantarum* with known probiotic properties decreased pain and flatulence in patients with IBS as taught by Nobaek in IBS patients with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification since Fearon teaches methods of increasing at least one Th1-associated cytokine in an individual, including IL-2, IL-12, TNF-beta, and IFN-gamma in an individual, by administering an effective amount of an IMO/MC complex to individuals having disorders which respond to the administration of IFN-gamma such disorders include a number of inflammatory disorders including, but not limited to, ulcerative colitis and particularly since Barbara et al teach that low grade mucosal inflammation in IBS due to an increased number of inflammatory cells in the colonic and ileal mucosa as a result of infectious enteritis and changes in bacterial microflora may all play a role in promoting and perpetuating this low grade inflammatory process and altered interactions between the mucosal immune system and the afferent nerve terminals which project into the intestinal mucosa has been found in patients with visceral hypersensitivity and in cases of IBS. One of ordinary skill in the art would have been sufficiently motivated to make a modification by use of antispasmodic agent, antidepressant, antidiarrheal, serotonin 5HT3 antagonist since Barbara et al teach the involvement of low grade inflammation in altered neuromotor function in IBS is also supported by the observation that in normal and inflamed intestinal mucosa immunocytes lie in close proximity to nerve fibres of the enteric nervous system and as this close anatomical relationship does not occur by chance, the existence of a functional interplay between neural and immune elements in the intestinal mucosa seems likely and furthermore, inflammatory cells are more strictly related to neurones supplying the bowel mucosa in IBS patients than in healthy subjects and altered neuroimmune interactions may play a role in sensorimotor dysfunction in IBS (p i43, 1<sup>st</sup> column).

Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 5, 7-8 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 9-14 of U.S. Patent No. 6,613,751. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods in both claims overlap in scope of having to treat IBS via a nucleic acid or the formula of 5'-CpG-3' in a subject. For example, claim 2 of the instant invention is directed to a method for the administration of a therapeutic nucleic acid comprising a nucleotide sequence of the formula 5'-CG-3'. US 6,613,751 also teaches A method for ameliorating gastrointestinal inflammation in a subject comprising: administering to a subject suffering from gastrointestinal inflammation a formulation comprising an immunomodulatory nucleic acid to the subject, the immunomodulatory nucleic acid comprising the sequence 5'-CpG-3', wherein said

immunomodulatory nucleic acid is isolated or synthetic, said administering being in an amount effective to ameliorate a symptom of gastrointestinal inflammation in the subject; wherein said administering is by a route selected from oral and subcutaneous, and wherein gastrointestinal inflammation is ameliorated in the subject. Thus, the claims of '751 differ only with respect to administering to the subject a 5'-CpG-3' for treating gastrointestinal disorders which IBS is one type of gastrointestinal disorders. However, in view of the teachings of '751 a 5'-CpG-3' is an obvious variant of 5'-CG-3', as taught in the specification of the instant invention.

Applicants argue U.S. Patent No. 6,613,751 claims a method of treating gastrointestinal inflammation. The instant claims are directed to methods of treating irritable bowel syndrome (IBS). IBS is not the same as gastrointestinal inflammation. A method of treating IBS is not an obvious variation of a method of treating gastrointestinal inflammation. As discussed in the instant specification, IBS is a functional bowel disorder for which there is currently no mechanical, biochemical, or overt inflammatory condition that explains the symptoms. Specification, paragraph 0004. Indeed, according to the National Institutes for Health, inflammation is not a feature of IBS. As such, IBS is a disorder that is distinct from "gastrointestinal inflammation." In keeping with this distinction, U.S. Patent No. 6,613,751 does not include IBS among the list of gastroinflammatory disorders.

These arguments are not persuasive because a gastrointestinal inflammation embraces irritable bowel syndrome. It is well known in the art and there is evidence of inflammation in the IBS. It is well known that IBS is associated with altered gastrointestinal physiology and hypersensitivity. For example, **Barbara et al**, [Gut, 51(Suppl I):i41-i44, 2002 (IDS)] note that low grade mucosal inflammation in irritable bowel syndrome (IBS) due to an increased number of inflammatory cells in the colonic and ileal mucosa as a result of episodes of infectious enteritis and changes in bacterial microflora may all play a role in promoting and perpetuating

this low grade inflammatory process (abstract). Barbara et al note altered interactions between the mucosal immune system and the afferent nerve terminals which project into the intestinal mucosa has been found in patients with visceral hypersensitivity and in cases of IBS (p 141, 2nd column, 2nd paragraph). Barbara also notes abnormal neuroimmune interactions may contribute to the altered gastrointestinal physiology and hypersensitivity that underlies IBS thus IBS is associated with intestinal inflammation and infections in the pathogenesis of IBS is given (abstract). Thus, the art teaches that gastroinflammatory disorders include IBS, therefore the rejection is maintained.

### ***Conclusion***

**No claim is allowed.**

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If

attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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